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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,649	10/15/2001	John E. Ford	28110/37665	7526

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/981,649	FORD ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendments of 22 May 2003 (Paper No. 11) and 28 February 2002 (Paper No. 3) have been entered in full. Claims 13 and 18 are amended and claims 81-83 are added. Claims 1-12 and 25-83 are cancelled.

Claims 13-18 are under consideration in the instant application.

Election/Restrictions

Applicant's election with traverse of the species "colon cancer cell" in Paper No. 11 (22 May 2003) is acknowledged. The traversal is on the ground(s) that the invention is drawn to a single method of detection. Applicant argues that the method of detection is the same regardless of cell type. Applicant submits that the specification discloses experimental data supporting the use of the polypeptide of the invention in detecting the claimed cancer types (pg 71, lines 11-21; pg 112-114, 116-119). Applicant indicates that it would not impose an undue burden of the examiner to examine the method claim with regard to the various cancer cell types. This is found to be persuasive. The species of cancerous cell has been rejoined.

Drawings

1. The corrected or substitute drawings were received on 28 February 2002 (Paper No. 6). These drawings are acceptable.

Specification

2. The abstract of the disclosure is objected to because in line 5, the phrase "is useful" should be amended to recite "are useful". Correction is required. See MPEP § 608.01(b).

3. The disclosure is objected to because of the following informalities:

3a. An updated status of the parent nonprovisional application should be included in the first sentence of the specification. A statement reading "This is a continuation-in-part of U.S. Application Serial No. 09/687,860, filed October 13, 2001, which is a continuation-in-part of U.S. Applicant Serial No. 09/363,316, filed July 28, 1999, U.S. Patent No. 6,392,019" should be entered. It is noted to Applicant that this objection will be maintained until the status of 09/687,860 changes or the instant application is deemed allowable.

3b. The Brief Description of Drawings for Figures 5 and 6 at pg 17 of the specification does not match Figures 5-6 submitted on 28 February 2002 (Paper No. 6). Specifically, the brief description for Figure 5 does not seem to match any of the Figures present in the application. It appears that a Figure may be missing. Furthermore, the brief description in the specification for Figure 6 seems to match the current Figure labeled "Figure 5".

3c. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (See for example, pg 111, line 5). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

3d. The specification at pages 116-119 repeatedly use the term "s". It is not clear what this letter is intending to abbreviate. The Examiner has interpreted "s" in the context of the sentences to stand for "sample".

3e. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "METHOD OF DETECTING A CANCEROUS CELL EXPRESSING AN EGF MOTIF PROTEIN".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 13-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a cancerous colon cell expressing the polypeptide of SEQ ID NO: 24 or a fragment that comprises at least amino acids 412-426 of SEQ ID NO: 24 in a biological sample, comprising (a) contacting the sample with an antibody or fragment thereof that specifically binds to the polypeptide of SEQ ID NO: 24 or a fragment that comprises at least amino acids 412-426 of SEQ ID NO: 24 for a time period sufficient to form a complex; and (b) detecting the complex, so that if a complex is detected it indicates the presence of the cancerous colon cell, and wherein the biological sample is a tissue or cell, does not reasonably provide enablement for a method of detecting a cancerous cell expressing the polypeptide of SEQ ID NO: 24 or a fragment thereof in a biological sample, comprising (a) contacting the sample with an antibody or fragment thereof that specifically binds to the polypeptide of SEQ ID NO: 24 or a fragment thereof for a time period sufficient to form a complex; and (b) detecting the complex, so that if a complex is detected it indicates the presence of the cancerous cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Briefly, the claims are directed to a method of detecting a cancerous cell expressing the polypeptide of SEQ ID NO: 24 or a fragment thereof in a biological sample, comprising (a)

contacting the sample with an antibody or fragment thereof that specifically binds to the polypeptide of SEQ ID NO: 24 or a fragment thereof for a time period sufficient to form a complex; and (b) detecting the complex, so that if a complex is detected it indicates the presence of the cancerous cell. The claims also recite that the polypeptide fragment comprises the amino acids 22-553 of SEQ ID NO: 24 or amino acids 412-426 of SEQ ID NO: 24. The claims recite that the antibody is conjugated to a radioisotope, affinity label, enzymatic label, or fluorescent label. The claims recite that the biological is selected from the group consisting of tissue, cell, blood, serum, lymphatic fluid, urine, and cerebrospinal fluid. Additionally, the claims recite that the cancerous cell is selected from the group consisting of a brain cancer, prostate cancer, breast cancer, skin cancer, lymphoma, sarcoma, colon cancer, leukemia, ovarian cancer, and pancreatic cancer cell.

The specification teaches that EGFL6 mRNA was detected in colorectal cancer tissues and therefore, it was of interest to determine if EGFL6 protein correlates with EGFL6 transcript expression in colorectal cancer tissue (pg 117, lines 15-17). The specification also teaches that fourteen colorectal cancers of various grades and stages and three normal colorectal tissues are fixed, cut, and incubated with an anti-EGFL6 polyclonal antibody (pg 117-118). The specification discloses that 71% of the colon carcinoma tissues are positive for EGFL6 protein expression (approximately 10 out of 14 samples), including the low grade samples (pg 119, lines 1-4). EGFL6 protein and mRNA expression are not detectable in any of the normal colon samples (pg 119, lines 4-5). The specification also indicates that an anti-EGFL6 primary polyclonal antibody is generated against the peptide QDREDDFDWNPADR (which corresponds to amino acids 413-426 of SEQ ID NO:24) (pg 126, line 28; pg 127, line 1). However, the

specification does not teach any methods or working examples that detect all cancerous cells expressing the polypeptide of SEQ ID NO: 24 or all possible fragments of SEQ ID NO: 24 in all possible types of biological samples. The specification does not teach detection of EGFL6 *protein expression* in any cancers, other than colorectal cancer tissue. Although the specification teaches that EGFL6 mRNA transcript is expressed in prostate cancer, breast cancer, colon cancer, lymphoma, sarcoma, and brain cancer (pg 114-117), the state of the art is such that protein expression levels cannot be accurately predicted from the level of corresponding mRNA transcript (Haynes et al., Electrophoresis 19:1862-1872, 1998). Haynes et al. studied 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript levels. Haynes et al. found that for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold (pg 1863, ¶ 2, Figure 1). The specification also seems to support these observations because three of the colorectal carcinomas negative for EGFL6 protein expression were found to express EGFL6 mRNA in the *in situ* hybridization analysis (pg 119, lines 6-7). Therefore, one skilled in the art cannot predict that the EGFL6 mRNA transcript levels determined in various cancerous tissues are indicative of EGFL6 polypeptide (SEQ ID NO: 24) expression in cancerous cells. Undue experimentation is required by the skilled artisan to detect EGFL6 polypeptide expression in all possible tumor tissues/cells, other than colon cancer.

Additionally, a large quantity of experimentation would be required of the skilled artisan to detect cancerous cells in any sample other than a cell or tissue. In Examples 6 and 8-9 of the specification, the *in situ* hybridization and protein expression studies are performed directly with normal and cancerous tissues. There are no methods or working examples in the specification to

indicate that the EGFL6 polypeptide of SEQ ID NO: 24 is present in blood, serum, lymphatic fluid, urine, or cerebrospinal fluid. Undue experimentation would be required of one skilled in the art to develop and carry out studies examining EGFL6 polypeptide expression in various body fluids other than cells or tissue.

Furthermore, regarding the claim recitation of any fragment of SEQ ID NO: 24 (for example, claim 13, line 2), the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is

merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Daniel et al. (Virology 202: 540-549, 1994) also disclose that primary amino acid sequences do not predict antigenic determinants and therefore, changing the amino acid sequence of a polypeptide may also affect antigenicity (pg 540, 547).

Additionally, the Examiner has interpreted claim 13 to encompass all possible fragments of SEQ ID NO: 24, including fragments of at least 1 amino acid. One skilled in the art cannot predict that all fragments of EGFL6 are exclusive to SEQ ID NO: 24. Non-specific polypeptide fragments of SEQ ID NO: 24 may overlap with the amino acid sequences of other proteins. Therefore, the skilled artisan would be not be able to determine if the polypeptide fragment-antibody complex detected in the claimed method truly indicates that cells are expressing the EGFL6 polypeptide of SEQ ID NO: 24. Furthermore, the non-specific fragment-antibody expression pattern may not be unique to only cancer cells.

Due to the large quantity of experimentation necessary to detect EGFL6 protein expression in all possible cancers other than colon cancer, to detect a cancerous cell expressing

the polypeptide of SEQ ID NO: 24 in all possible biological samples other than cells and tissue, and to generate and detect the infinite number of fragments of SEQ ID NO: 24, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to same, the complex nature of the invention, and the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the unpredictability of correlating mRNA transcript levels to protein expression, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 13-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 13-18 are rejected as being indefinite because use of the phrase "or fragment thereof" for both the polypeptide of SEQ ID NO: 24 and an antibody is confusing.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure (EGFL6):

Ford et al. U.S. Patent 6,392,019

Ford et al. U.S. Patent 6,392,018

Greener M. Mol Med Today. 2000 Apr;6(4):139-40.

Yeung G et al. Genomics. 1999 Dec 1;62(2):304-7

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C Kemmerer

BEB
Art Unit 1647
July 18, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER